



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Roberts
Serial No. 09/775,909
Filed: February 2, 2001
For: VACCINE
COMPOSITIONS

DECLARATION

I, Mark Roberts, declare as follows:

1. I am the inventor of this patent application. I currently hold the position of Professor of Molecular Bacteriology, Institute of Comparative Medicine, Faculty of Veterinary Medicine, University of Glasgow, Bearsden Road, Glasgow G61 1QH, UK. My Research interests are focused on understanding, at the molecular level, the mechanisms by which pathogens cause disease and the nature of the immune response to them. A copy of my curriculum vitae is attached as Exhibit 1.
2. I have been asked to comment on the Examiner's rejection of certain claims as being unpatentable (obvious) over Wilson et al in view of Nencioni et al, as set forth on pages 5 and 6 of the Official Action of 19 April 2004. I confirm that I have read the Official Action, the patent application, and Wilson et al and Nencioni et al.
3. My main comment is that it cannot be concluded from Wilson et al that the adjuvant activity of pertussis toxin is independent of the enzymatic activity of the toxin. There are two reasons for this.
4. The first reason derives from the fact that pertussis toxin produces a myriad of biological effects by catalysing the ADP-ribosylation of many different G proteins (Ui, 1988, The multiple biological activities of pertussis toxin, In Pathogenesis and immunity in pertussis, edited by A.C. Wardlaw and R. Parton, pages 121-145, Exhibit 2). Wilson et al tried to examine just one of these effects, namely the elevation of cAMP levels. Thus, even if Wilson et al did show that elevation of cAMP has no effect on adjuvant activity (which they did not for reasons which I explain below), this would not allow any conclusion to be drawn that the adjuvant activity of pertussis toxin is independent of its enzymatic activity. The most that could be concluded is that the adjuvant activity of pertussis toxin is probably mediated through an effect of its enzymatic activity different from its effect on cAMP levels. This is recognised in the last paragraph of the Discussion section of Wilson et al, where it is stated that:

Although this experiment is a rather blunt probe of immune regulation we consider that CT and PT may act by an alternative mechanism, such as via a common G protein-mediated effect not involving enhancement of adenylate cyclase activity.

5. Thus, even the authors of Wilson et al recognise that, even if their results are taken at face value, the effect of pertussis toxin on immune regulation is likely to derive from a G-protein mediated effect (i.e. an enzyme-mediated effect) of the toxin not involving elevation of cAMP. In other words, the authors recognise that the effect of pertussis toxin on immune regulation is likely to derive from one of the myriad of non-cAMP related effects resulting from the enzymatic activity of pertussis toxin.
6. The second reason why it cannot be concluded from Wilson et al that the adjuvant activity of pertussis toxin is independent of the enzymatic activity of the toxin is that Wilson did not in fact show that they had any produced any effect on cAMP levels. The relevant experiment described in Wilson et al involves feeding forskolin to mice. Forskolin is known to raise cAMP levels in cultured cells *in vitro*. However, Wilson et al does not show that feeding forskolin to mice produces elevated cAMP levels or has any other relevant effect. All that Wilson et al showed was that the mice got sick. They did not show that feeding forskolin had any relevant effect on the immune function of the mice.
7. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardise the validity of this Declaration, the patent application, or any patents issuing thereon.

Declared this 16 day of September 2004


Mark Roberts